DRAWING AMENDMENTS:

Figure 2 is amended to correct several typographical errors.

A marked up version of Figure 2 showing the proposed Figure changes is attached at Appendix A of this Reply.

A "Replacement Sheet" for Figure 2 is attached at Appendix B of this Reply.

REMARKS

Claims 1-5, 7-11 and 13-17 are pending in the application.

Claims 1-2, 7-8, and 13-14 are amended above to more clearly set forth what the Applicant regards and their invention.

The specification is amended above to correct a drawing reference.

Figure 2 is amended herein to correct grammatical errors.

No new matter is added to the application by way of these amendments.

I. CLAIM 14

The Final Rejection does not mention claim 14. Moreover, claim 14 was not rejected over the prior art in the January 30, 2009 Office Action for this case. Therefore, the Applicant is uncertain if the claim stands rejected or if it is allowed. Regardless, claim 14 is believed to be patentable at least by virtue of it dependence upon claim 13 which is novel and patentable at least for the reasons recited below.

II. THE ANTICIPATION REJECTION TRAVERSE

Claims 1, 3-5, 7, 9-11, 13 and 15-17 stand finally rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al.. "A parallel approach to tubule grading in breast cancer lesions and its VLSI Implementation", Computer-based Medical Systems, 1991. Proceedings Of The Fourth Annual IEEE Symposium Baltimore, MD, USA 12-14 May 1991, Los Alamitos, CA, USA, IEEE Comput. Soc, US (12-05-1991), 322-329, XP-10024202 (submitted on IDS filed 7/25/2005, hereinafter "Cheng"). In order for a reference to anticipate, the reference must show the same invention in as complete a detail as claimed. *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Moreover, the elements must be arranged in the reference as required by the claim. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

Claims 1, 7 and 13 are independent claims. Claims 1, 7 and 13 paragraphs a) and b) have been amended to make it clear that the second and third images distinguish first and second objects respectively (as shown in Figures 4 and 5). Paragraph a) of claims 1, 7 and 13 have also been amended to emphasise the fact that first object size is associated with potential tubules.

Paragraph c) of claims 1, 7 and 13 have been amended to specify that the step of combining data from the second and third images is implemented by excluding objects not indicated to have epithelial layers and first objects not containing second objects. This is based on Applicants' specification at page 11 line 16 to page 12 line 8. For purposes of the Reply, independent claims 1, 7 and 13 will be discussed together and referred to collectively as claim 1 unless otherwise indicated.

A. The Applicant's Invention

Applicants' invention will now be briefly reviewed to assist in understanding the differences between the invention and the cited art (this review does not prevail over the patent claims, which alone define the invention). The invention involves:

a) a histological first image (see Figure 3);

b) processing the first image to yield a second image: this second image contains potential tubules, i.e. objects exhibiting tubule-like size and pixel values near and at boundaries indicating epithelial layers (see Figure 4 with filled-in tubule holes);

c) processing the first image once again but in a different way to yield a third image: this third image contains features with pixel values indicating fat and holes (72 in Figure 5); and

d) combining data from the second and third images - see Figure 6, which results from multiplying together like-located pixels in the second and third images: this shows only features common to the second and third images, i.e. isolated tubule holes 81 (52 in Figure 3). Figure 6 does not show fat (55 in Figure 3), objects without holes (53 in Figure 3) or tubule epithelial outer layers (51 in Figure 3). Identifying tubule holes also identifies the tubules containing those holes – compare Figures 4 and 6.

B. The Cheng Reference

The examiner states that the Cheng Abstract teaches a method of grading tubules in digitized images of microscopic slides, reading on to the preamble of Applicants' method claimed in claim 1. Cheng at page 323, part B teaches locating bright areas by comparing a threshold T_b with a median-filtered pixel intensity $I_m(i,j)$ at pixel i,j (NB Cheng states I(i,j) *etc.* is

an image, whereas it is clearly an intensity of a single image pixel at location i,j for consistency with the text: e.g. pixel intensity values are given for $I_b(i,j)$ at part B page 323): this produces a binary pixel intensity $I_b(i,j)$ of 1 or 0 according to whether or not $I_m(i,j)$ is greater than T_b.

Cheng does not read on to claim 1(a), because there is no disclosure of forming a second image of objects which are potential tubules – this is simply reading Applicants' invention into Cheng instead of deriving it from Cheng. Cheng part II, page 323 and part C, page 324, last paragraph, first sentence collectively indicate that tubules are lighter areas surrounded by circular dark boundaries: Applicants do not dispute that tubules appear as lighter areas surrounded by dark boundaries, and in fact they state this in their patent specification at page 7 line 16. A tubule is not the invention which is claimed by Applicants. Instead, as indicated in Applicants' specification at page 7 lines 12-22, the invention seeks to identify tubules.

Moreover, Cheng is wrong in stating that tubules have circular boundaries, because a tubule is an image of a section (a cut) through a mammary duct. It can appear round, oval, cylindrical or irregular depending on the angle of the section to the duct axis and the shape of the duct after being cut (see Applicants' specification at page 7 lines 12-22). This is an important point because it bears on the issue of whether or not Cheng is workable, and it would seem that Cheng is in fact unworkable because of it.

Unlike claim 1(a), Cheng does not disclose forming an image of potential tubules. Instead of making an image of potential tubules, Cheng sets out to detect the boundaries of holes in tubules. Cheng does not even detect the outer boundary of the tubule epithelial layer. The reasons for this are as follows: Cheng begins by locating a bright (white/high intensity) pixel in an imaged bright core with intensity corresponding to a tubule hole pixel and converts it to a binary intensity $I_b(i,j)$ (step B page 323). Cheng then classifies bright areas as tubules or non-tubules (step C pages 323 to 326) by looking for boundaries of holes in tubules with radii between minimum and maximum values R_{min} and R_{max} provided by experts. This is done by performing Laplacian calculations on pixels, because the Laplacian is large for a boundary and small otherwise (step C first paragraph page 323/324).

Clearly, Cheng must calculate a series of Laplacians for every bright object in an image with a radius not less than the minimum value R_{min}. This means that whole series of Laplacians (not just one) are calculated unnecessarily for objects such as fat which are not tubules, which wastes

processing capacity. In this regard, a series of successive Laplacians is calculated for an object until the maximum tubule radius R_{max} is reached and no epithelial layer has been detected. Applicants' invention avoids this problem by producing an image distinguishing potential tubules and another image distinguishing fat and holes. In Applicant's invention, combining these two images identifies tubules.

In order to scan over an area to locate a boundary, Cheng performs an extension operation (page 324 *Definition 2*) upon the bright pixel to get its neighbouring pixels and iterates this operation until the prearranged minimum tubule hole radius R_{min} is reached (last paragraph page 324 and page 325 at 1.). The Laplacian calculations are then performed on all pixels distant R_{min} from the bright pixel, thresholded and the results used to provide tubule flags for pixels (page 325/326 at 2. to 11.). The extension operation and Laplacian calculations are iterated until the prearranged maximum tubule hole radius R_{max} is reached or the Laplacian value is large indicating a tubule boundary (page 325 lines 1-5).

Cheng performs each Laplacian calculation upon one small image region at a time, not upon the whole image or all objects in the image of a particular kind, i.e. tubules or fat and tubule holes. In this regard please see Cheng page 325 at 3., which states "All the pixels which are in the most outer layer of the extension carry out the Laplacian operations". Consequently only a layer of pixels is involved at a radius in the range R_{min} to R_{max} from the bright pixel, not the whole image or objects in it.

Cheng therefore discloses the following:

e) a histological first image – "input image", page 323, Section II, preamble, last sentence;

f) processing the first image to yield a second image with pixel intensities $I_m(i,j)$ and which has been median filtered (part B, preamble) to reduce noise - Section II, preamble, second sentence;

g) processing the <u>second</u> image (not the first) to yield a binary third image with pixel intensities $I_b(i,j)$ - part B last line;

h) performing Laplacian calculations on pixels in a layer at a radius in the range R_{min} to R_{max} from a bright pixel in the binary <u>third</u> image (not the first), until the

maximum tubule hole radius R_{max} is reached or the Laplacian value is large indicating a tubule boundary (page 325 lines 1-5);

i) successive stages in processing an image: each image is used once and then discarded (treating the iterative process of image extension and Laplacian operation as one "use" as it is merely detection of a single feature, a boundary); and

j) counting non-zero pixels to indicate tubule area – part D lines 1-4: this counts pixels within a tubule boundary, i.e. tubule hole pixels.

C. Differences Between The Claimed Invention And Cheng

Based upon the summary of the invention and the summary of the Cheng reference teachings above, the claimed invention is novel and patentable over Cheng at least because, regarding claim 1 et al, Cheng does not disclose:

k) processing the first image twice, i.e. in two different ways, to yield second and third images distinguishing different types of image feature (claim 1 paragraphs a) and b));

l) combining data from the second and third images to identify as holes within tubules second objects contained within first objects by excluding objects not indicated to have epithelial layers and first objects not containing second objects; and

m) since Cheng only counts tubule hole area, it does not count potential tubules ("first objects") or the area of the tubule epithelial layer, or distinguish single holed tubules from multi-holed tubules. Unless fortuitously and by some undisclosed means Cheng only receives histological specimens in which multi-holed tubules are absent, Cheng cannot:

   i) count the number of tubules,

   ii) express the number of tubules as a proportion of the number of potential tubules,

iii) determine the ratio of the area of each tubule hole to that of its respective tubule,

iv) determine the ratio of tubule hole total area to tubule total area, or

v) count tubules containing at least medium sized holes. Cheng therefore cannot carry out any of the tests claimed in claim 1 paragraph d) sub-paragraphs i) to v).

As previously discussed, Cheng does not read on to claim 1 part a). The examiner states that Cheng reads on to claim 1 parts b) and c), justifying this by stating that page 323, step C and page 324 teach a method of making a third image wherein each of the first identified objects potential tubules, i.e., are further analyzed to identify pixel values of likely tubules. It is respectfully submitted that this is quite wrong. It is wrong firstly because there is no identification of pixel values of likely tubules because this is known in advance – Cheng page 323 Section II preamble lines 2-6. It is wrong secondly because Cheng does not analyse whole objects which are potential tubules – instead Cheng analyses and performs extensions (page 325) upon centre pixels referred to as "bright cores" (page 323 Section II preamble lines 4-6). For each of these reasons, all rejected claims are novel and patentable over Cheng.

The examiner also takes the position that Cheng reads on step b) because the pixel values which indicate a potential tubule are also pixel values characteristic of fat and holes, i.e. rough textures, and cites Cheng page 324 last paragraph for tubules and rough textures both comprising homogeneous areas, stating the pixel values of the homogeneous areas of tubules reads on to the pixel value characteristics of fat and holes. The examiner's position is without merit and confuses two different issues. The examiner's position lack merit because the pixel value characteristics of fat and holes are alike, see Figure 5 of Applicants' specification where regions 72 indicate both fat and holes in tubules, but the pixel value characteristics of tubule epithelial layers are quite different to those of fat and holes – see Applicants' specification at page 7 line 16 and Cheng page 324 last paragraph last three sentences, referring to tubule bright cores and dark boundaries. The examiner's position confuses issues because the issue is not the similarity or otherwise between the pixel value characteristics of fat, holes and tubules, but instead the nature

of the objects which appear in the second image (potential tubules) and the third image (fat and holes), and which the examiner fails to mention.

The examiner also states that the analysis taught by Cheng step C is performed on the initial first objects wherein the first objects are potential or likely tubules and whose pixel values are characteristic of fat and holes. But in claim 1a) potential or likely tubules are not selected from having pixel values which are characteristic of fat and holes. They are instead selected from having pixel values which are characteristic of epithelial layers and quite different to those characteristic of fat and holes (see also above re "dark boundaries").

Referring to page 326 step D, the examiner contends that Cheng teaches a method of counting the tubule areas. However, as previously discussed, Cheng only counts tubule hole area and not potential tubules ("first objects") or the area of the tubule epithelial layer surrounding the tubule hole(s), nor does it distinguish tubules with single holes from tubules with multiple holes. Consequently, as has been said, Cheng does not read on step d), substep ii), step e), or step f). For these reasons as well, all pending claims are novel and patentable over Cheng.

Claims 3, 9, and 15 are independently novel. Claims 3, 9 and 15 relate to the third image which distinguishes second objects with pixel values indicating fat and holes: the claims relate to this image being binary. Cheng discloses binary images but does not disclose a binary image which distinguishes second objects with pixel values indicating fat and holes.

Claims 4, 10 and 16 are also independently novel. The examiner states that Cheng teaches claims 4, 10 and 16 at page 328. It is respectfully submitted that this statement is entirely lacking in foundation. Claim 4 (similarly claims 10 and 16) relates - broadly speaking - to combining data from the second and third images either by multiplying second image pixels by respective like-located third image pixels, or by logically ANDing together such pixels.

Cheng page 328 contains no mention whatsoever of:

n) a second image associated with potential tubules (as per claim1a)), or

o) a third image associated with fat and holes within tubules (as per claim1b)), or

p) combining data from the second and third images by multiplying or logically ANDing together like-located second and third image pixels.

Claims 5, 11 and 17 are further independently novel. Regarding claims 5, 11, and 17, the examiner states that Cheng page 326 step D, teaches grading tubules comparable with that of a physician, i.e. a medical expert as claimed. Here again it is respectfully submitted that this statement is entirely lacking in foundation. In this regard, the only reference to a physician in Cheng step D is in the first and second lines, which state "... for physicians to obtain a score based on tubule grading, they require the total amount of tubule area. This merely states what physicians require not what they do – it contains no disclosure relating to whether the step D tubule grading is or is not comparable with that obtainable by a medical expert.

D. Cheng Does Not Enable The Claimed Invention

Applicants' invention possesses important technical advantages over Cheng. As has been said, Cheng is limited to circular tubule holes with radii in a predetermined range, R_{min} to R_{max}. Here Cheng is quite wrong technically, because a tubule can appear round, oval, cylindrical or irregular depending on the angle of the section to the duct axis and the shape of the duct after it is cut. Cheng does not deal with or even recognise the fact that tissue specimens are cut from tissue and tubule shape is dictated by the cutting process. Therefore, Cheng does not enable the claimed invention.

In order to anticipate a prior art disclosure must be enabling. To enable, an allegedly anticipatory reference must teach one of ordinary skill in the art how to carry out the claimed invention without undue experimentation. *Minnesota Mining and Manufacturing Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301, 64 USPQ2d 1270, 1278 (Fed. Cir. 2002). A reference is not enabling where it merely names or describes the desired subject matter without describing how it can be produced without undue experimentation. *Elan Pharmaceuticals, Inc. v. Mayo Foundation for Med. and Educ. Rsch.,* 346 F.3d 1051, 1055 (Fed. Cir. 2003).

It would seem that Cheng is not enabling for normal histopathology tubule specimens which have variable and possibly irregular tubule shapes. This is because Cheng relies on selecting successive circles of pixels ("at a most outer layer" page 324 third line from bottom) increasing in size in an image and obtaining a large Laplacian value when a circle lies on a boundary, see page 324 last two sentences. Clearly, a pixel circle cannot match an oval, cylindrical or irregular tubule. A best, a pixel can only match a part of such a tubule's circumference having the appropriate radius. Moreover, differently radiused pixel circles will

match different parts of that circumference. Consequently, instead of getting a sharp change from high to low in the resulting Laplacian to locate a tubule boundary, one will get a series of intermediate Laplacian values spread out over a variety of pixel circles and it will not be clear that a tubule has been located.

Furthermore, Cheng discloses using pixel circles centred on holes and extending the circles outwardly to find a boundary indicated by a large charge in Laplacian. This results in each hole being treated as belonging to a different tubule. A tubule may have more than one hole and Applicants' invention can be adapted to correct the tubule count for this whereas Cheng cannot. All pending claims are therefore novel and patentable for this reason as well.

CONCLUSION

The pending application claims are believed to be ready for patenting for the reasons recited above. Favorable reconsideration and allowance of all pending application claims is courteously solicited.

Date: October 27, 2009

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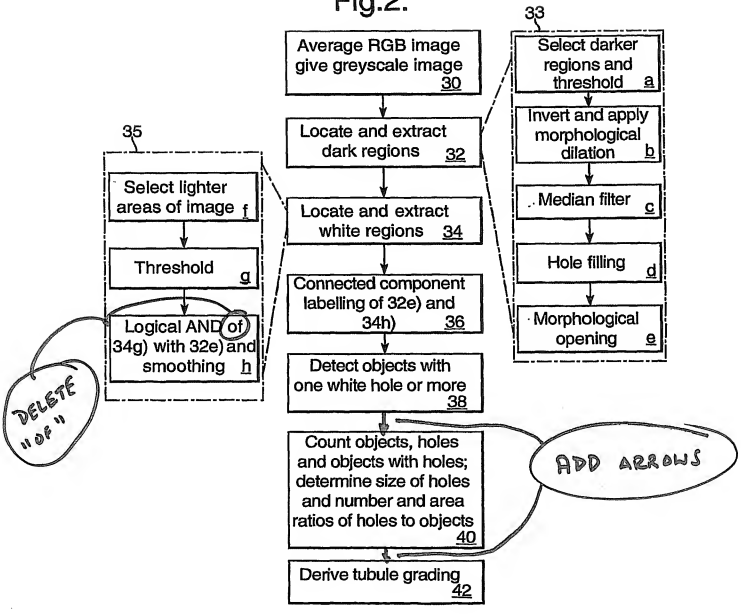
Appendix A

(Figure 2 – Marked Up With Proposed Changes)

Fig.2.


Average RGB image give greyscale image 30
Locate and extract dark regions 32
Locate and extract white regions 34
Connected component labelling of 32e) and 34h) 36
Detect objects with one white hole or more 38
Count objects, holes and objects with holes; determine size of holes and number and area ratios of holes to objects 40
Derive tubule grading 42
33
Select darker regions and threshold a
Invert and apply morphological dilation b
Median filter c
Hole filling d
Morphological opening e
35
Select lighter areas of image f
Threshold g
Logical AND of 34g) with 32e) and smoothing h
DELETE 11 OF 11
ADD ARROWS

Appendix B

(Figure 2 – "Replacement Sheet")